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Award Number: W81XWH-09-1-0673

TITLE: IL-6 Receptor Isoforms and Ovarian Cancer

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REPORT DATE: October 2011

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE October 2011		2. REPORT TYPE Annual		3. DATES COVERED 15 September 2010 – 14 September 2011	
4. TITLE AND SUBTITLE IL-6 Receptor Isoforms and Ovarian Cancer				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-09-1-0673	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Susan E. Waltz E-Mail: susan.waltz@uc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Cincinnati Cincinnati, OH 45221				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT During the transition research period, we have purchased and are in the process of generating colonies of mice containing an IL6 Receptor (IL6R) knockout, liver and myeloid specific deletions of IL6R, and colonies with appropriate control mice. We have obtained and are generating the in house breeding colonies and have initiated measures for genotyping and increasing the numbers of experimental mice. Our goal is to generate these colonies of mice to complete experiments outlined in Specific Aim 2 related to determining the relative contributions of host IL6R to angiogenesis, cell survival and host survival of cancer cell lines in vivo.					
15. SUBJECT TERMS IL-6 Receptor, inflammation, ovarian cancer, metastasis					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
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Introduction

The overall goal of the proposed study has been to test the hypothesis that membrane and soluble IL6R play distinct roles in driving tumor progression, angiogenesis. Two major Tasks were funded as outlined in the Statement of Work which encompass examining IL6R expression in ovarian patient tumor samples and performing experiments to define the function of IL6R in the tumor proper and host microenvironment.

Body

The overall goals have been accomplished and the data published related to Task 1 (1). Task 1 entailed the "Identification of IL6R isoforms in patient samples." In the reported studies, elevated levels of IL6, total IL6R, differential spliced forms of IL6R, ADAM10 and ADAM17 were found in ovarian tumors. In addition, these studies further demonstrated that both tumor and host cells contribute to soluble IL6R expression in the tumor microenvironment.

Task 2 entailed "In vivo experiments to determine functions of IL6R isoforms and tumor:stroma relationships. For this task, mouse breeding colonies and genotyping procedures were set up. A recent paper was also published related to the characterization and general phenotype of these mice (2). Preliminary xenograft studies suggested that host IL6R may be an important means by which IL6R levels are increased in the tumor microenvironment along with the importance of IL6R in the tumor proper. At this point, the project was halted as the initial PI left the institution. A few months later, a new PI was designated and has started to re-initiate the mouse breeding colonies which were unfortunately sacrificed prior to the designation of a new PI. The new PI will pursue and continue experiments designated in Task 2 with a focus on in vivo experiments to examine the significance of host IL6R in tumor growth and metastasis.

Key Research Accomplishments

- Staffing accomplished to support continuation of project.
- Obtained IL6R floxed mice (IL6R^{ff}), IL-6R deficient mice (IL6R^{-/-}), LysMCre and AlbCre mice.
- Initiated breeding colonies to generating control and experimental animals.
- Initiate procedures to successfully genotype mice from breeding colonies.

Reportable Outcomes

Cell lines:

Obtained ES-2 and Skov-3 cell lines with overexpression of IL6R, knockdown of IL6R and controls.

Gene Targeted Animals:

Have obtained and are generating breeding colonies for IL6R^{-/-}, and IL6R^{ff} mice along with LysMCre and AlbCre mice to generate conditional deletions of IL6R in myeloid cells and hepatocytes respectively.

Research opportunities provided for individuals based on studies in this award:

William D. Stuart, Principal Research Scientist

Conclusion

Since the last reporting period, we are unable to generate any further conclusions based. Since the last reporting period, Dr. Angela Drew, the prior PI on this application, left the University of Cincinnati. Subsequently, the new PI, Susan Waltz, has taken over the remaining goals of the proposal. During this transition time, the new PI has become familiar with the prior progress on the grant and has started to garner the resources and reagents necessary to complete the task which had not been accomplished (primarily associated with Aim 2 of the funded application). Due to this transition, the new PI has also requested, and was granted, a one year no cost extension to continue this work.

References

1. Rath KS, Funk HM, Bowling MC, Richards WE, Drew AF. Expression of soluble interleukin-6 receptor in malignant ovarian tissue. *Am J Obstet Gynecol.* 2010;203(3):230 e1-8.
2. McFarland-Mancini MM, Funk HM, Paluch AM, Zhou M, Giridhar PV, Mercer CA, et al. Differences in wound healing in mice with deficiency of IL-6 versus IL-6 receptor. *J Immunol.* 2010;184(12):7219-28.

Appendices

None